28 (New) The method of claim 23 wherein said autoantigen is administered to said host orally.

REMARKS

Reconsideration of this application is respectfully requested.

By the present amendment, all claims except 23 through 26 are cancelled without prejudice or disclaimer. The Examiner has indicated that claim 23 is in the case and under examination. Claims 24-26 have been amended so that all independent claims require oral or entered administration of an antigen and all claims require autoimmune response suppression. Claims 27-28 are new.

Support for this amendment is self-evident.

Claim 23 adopts a portion of autoantigens as explained in the present specification at p.6, lines 16-20; p.4 lines 25-27; p.6, lines 2-6 and p.4 lines 16-17 and p.6 lines 13-15. See Amendment mailed June 30, 2000 paragraph bridging pp. 4-5. Claim 23 specifies that the autoantigen need not come from the same individual as is being treated. This is consistent with the illustration of the term autoantigen in the specification as an antigen that induces a model for the disease in the field.

All claims now require abatement of an autoimmune response. This should end speculation about prevention vs therapy and should leave no doubt as to who is to be treated: persons having an autoimmune response associated with myastheria gravis.

All reference to antigen fragments has been eliminated from claim 24. This was done only to expedite prosecution and without conceding the correctness of the

Examiner's position.

Claims 26-28 are directed to the preferred route of administration.

Enablement

In response to the rejection of claims 23-26 under 35 USC §112 first paragraph ("enablement rejection") applicants submit as follows:

It is applicants' understanding that the Examiner's enablement rejection has to do with his doubts about whether the treatment would be effective only if orally administered before there is any abnormal autoimmune response and whether the treatment would be effective given that in human beings (i) the disease initiating antigen may not be known and (ii) the autoantigens may be many ("determinant spreading"). However, the cited references Zhou Tong ("Zhou") and Tisch do not support the Examiner's position, and there is thus no evidence of noenablement.

Zhou Tong does not administer any autoantigen and does not administer any antigen by oral route. Zhou Tong administers dextran, not an autoantigen, and does so only by injection intraperitonally (p. 1628 left col. paragraph 2.3) not by oral route.

Because as Tisch shows (and will be explained below) the mechanism of tolerance varies according to the mode of administration, Zhou Tong's findings are not applicable to the present invention, regardless of whether Zhou Tong shows or does not show failure to suppress disease by injecting an antigen after commencement of the abnormal immune response. Hence the findings of Zhou cannot be used to support the Examiner's position.

More important, a failed experiment is not significant in immunology unless it can be repeated and/or backed by a strong working hypothesis. Thus, the present inventors succeeded after others had failed in inducing oral tolerance in EAE by administering antigen after immunization (Example 2 and Table II of the present specification). The inventors developed a strong working hypothesis that permitted them to postulate a mechanism for oral tolerance other than clonal anergy or deletion which is the form of tolerance induced by injection. This working hypothesis of the inventors was backed by two types of data. First, a fragment of MBP that was known to be unable to induce disease successfully induced tolerance when orally administered as described in Example 6 at pp. 35-36 of the present specification, and Table V. Second, the animals could be be tolerized even after immunization. The first set of data foreclosed anergy and clonal deletion as the mechanism. Both sets of data increased the likelihood of applicability to humans, and to many autoimmune diseases because the postulated mechanism of oral tolerance did not depend on direct encounter between a T cell and an antigen and did not depend upon the T cell encountering the very antigen which it recognized.

Zhou Tong which deals with <u>injection</u> of an antigen and with tolerance by anergy/clonal deletion cannot refute the inventors' data. The routes of administration are different and the mechanisms of oral tolerance are recognized as being different. See Tisch discussion.

Nor does the fact that the inventors' experiments were conducted with EAE

detract from the generality of their findings. The immune system of healthy mice does not know which model of which disease will later be induced. Hence, the experiments with pre-immunization feeding support generality of oral tolerance as an approach to disease treatment. Moreover, the inventors did try various disease models, EAE and adjuvant arthritis, and thus the specification is not vulnerable to criticism for disclosing a single species.

The portion of the Tisch et. al. relied on by the Examiner is similarly not directed to oral tolerance but is concerned exclusively with tolerance induced by injecting the antigen. This is made clear by the publications cited through p. 437 right column third whole paragraph as references in the Tisch article (see also direct reference to intraperitoneal injection at p. 437 middle column).

Indeed, it is well-known that anergy and clonal deletion require direct encounter of the antigen with the T cell recognizing the same antigen and this is precisely why knowledge of the autoantigen is essential when the anergy/clonal deletion mechanism is utilized as a tolerance pathway. This is the reason that in discussing tolerance induced by anergy or clonal deletion (i.e. by injection) the authors of Tisch et. al. express scepticism.

The tone of the Tisch article however is much more optimistic when it discusses oral tolerance at p. 438 starting with the first half of the second column. The grounds for scepticism do not exist. Tisch acknowledges that oral tolerance is different from anergy/clonal deletion.

Nowhere does Tisch suggest that the autoantigen needs to be known for oral tolerance to work. On the contrary, the Tisch authors acknowledge that knowledge of the initiating autoantigen is not necessary (Tisch p.438, middle col.)

Nowhere does Tisch suggest that immunization by oral administration of antigen is dangerous. To the contrary, Tisch states (p.438, middle column) that oral administration of antigen appears to be nontoxic.

The Examiner will appreciate that the Tisch commentary is by competitors of the present inventors, yet it is quite cognizant of the present inventors' contribution to reducing autoimmune response, which is what the present claims require. Hence, Tisch is supportive of applicants' position.

As stated above, the present invention does not work solely or even primarily by anergy or clonal deletion, which is the subject of Tisch's criticisms, but by active regulation of cells that contribute to an abnormal immune response. This has been demonstrated by the present inventors by the experiments described at Example 6 in which it was shown that antigen fragments <u>other</u> than the fragment that induces disease in an animal nevertheless suppress autoimmune-like response. Because of this, the Examiner's fears are not well-founded. The Example 6 data are not limited to EAE because the noninducing antigen was fed pre-immunization and thus reflects a general immune system phenomenon and not one confined to a particular antigen or disease state.

Nor is it necessary to make this showing with all autoimmune diseases in order

to establish the generality of a finding. The inventors postulated a cell-mediated suppression mechanism and showed that such a mechanism was at work in an autoimmune disease subjected to oral tolerization. This raised the expectation of success for the present invention. Indeed, in the present specification, tolerance was elicited after immunization with the disease causing antigen, and tolerance was elicited whether the antigen was the disease causing antigen or not. These findings were powerful findings that were not available to others, were not limited to a particular antigen or disease and were thus applicable to a genus of autoimmune diseases, permitting the present inventors to generalize their findings to other autoimmune diseases.

These findings were due to the nature of the immune system of mammals and do not have anything to do with the particular autoimmune disease. Indeed, T cells respond to antigenic stimulation whether the subject has autoimmune disease or not.

Nor are the findings limited to a particular antigen. The same findings were observed with MBP and MT, two very different antigens.

Additionally it has long been known that when animals and humans ingest food they do not mount an immune response to antigens found in the food. Indeed, even persons with autoimmune disease, even advanced disease, successfully tolerize themselves to food antigens, even food antigens their immune system has not seen before.

The present inventors, through their experiments in autoimmune disease,

brought together a new approach to treating abnormal autoimmunity with the body of knowledge that had already been developed about elicitation of tolerance to food. Thus, the inventors did not have to try their experiments in every autoimmune disease. They were able to generalize their conclusions by grouping their own results (successful tolerization post-immunization and successful tolerization using nondisease causing antigen fragment) together with those of others (active suppression mechanism of oral tolerance to food antigens) to conclude persuasively that the general phenomenon of tolerance to ingested antigen could be harnessed to suppress autoimmune response.

In the foregoing context, the Examiner's fears articulated at p.4, of the November 28, 2000 Office Action appear to be unfounded:

If the suppressive mechanism is not exclusively or even primarily clonal deletion or anergy, then a failure of the antigen to survive proteolytic degradation or to be absorbed or to cross the mucosa is not of concern unless the primary suppression mechanism depends on the antigen having such properties. As the inventors demonstrated, oral tolerance clearly does not. The inventors demonstrated this using two drastically different diseases (EAE and adjuvant arthritis) and two drastically different antigens (myelin basic protein and mycobacterium tuberculosis). Tisch is not inconsistent when it discusses oral tolerance.

Nor is the Examiner's fear of an adverse reaction to oral antigen well-founded. In all the studies conducted in autoimmune disease antigen ingestion proved to be

safe, and Tisch also supports this. Moreover, as stated above, even autoimmune disease patients in advanced states of disease successfully tolerize themselves to foods, so no added risk is gleaned from induction of oral tolerance to foods.

Lastly, immunology routinely requires more experimentation than other disciplines, and this should not be held against the applicants.

For all these reasons, namely the failure of the references cited by the Examiner to discredit the data or the working hypothesis of the present inventors, and the inventors' ability to elicit data and postulate a mechanism independent of knowledge of the antigen that causes or initiates disease, the present claims have not been shown to have failed to satisfy the enablement requirement. Hence the rejection should be withdrawn.

Written Description

In response to the written description rejection, applicants submit as follows:

The Examiner has concluded with respect to all claims, including claims 23-25, that they encompass more than what was described in the specification. The written description in this specification, however, does a lot more than is reported in the Office Action:

1. The specification contains experiments with EAE using whole myelin as the fed antigen.
2. It contains experiments with EAE (a model for the central nervous system autoimmune disease multiple sclerosis) using only nonencephalitogenic

fragment of myelin basic protein as the fed antigen, which showed that it was not necessary to feed the same antigen that the disease inducing cells would recognize.

3. It contains experiments with suppression of EAE using encephalitogenic fragments of myelin basic protein as the fed antigen.

4. It contains experiments with suppression of adjuvant arthritis, a model for a different autoimmune disease rheumatoid arthritis which affects joints, using MT as the fed antigen.

5. It predicts that many diseases could be treated by abatement of an autoimmune response using antigens administered orally.

6. It contains examples of feeding antigen after immunization or simultaneously therewith.

7. It defines autoantigens as including antigens which induce animal models for the disease as well as antigens which should be considered "self" by the immune system but are not.

8. It both names and claims myasthenia gravis as one of the diseases to be treated. See, e.g. the original claims.

The collective effect of these eight points is that the inventors have shown themselves to have been in possession of a general approach for suppressing an autoimmune response and to have explicitly stated that it would apply to myasthenia gravis. This is a very different situation than Amgen or Fiers which the Examiner has

relied on, as will be explained further below.

In addition to the foregoing eight points, the prior art contains plenty of references to a single antigen that induces a model for myasthenia gravis. Thus, at least claim 23 is fully described since it recites an autoantigen that induces a model for MG. Claim 23 is also fully described because the inventors adduced evidence that the claimed approach is a general approach and that it worked with the vastly different diseases EAE and adjuvant arthritis; and that worked whether the feedings occurred prior or subsequent to challenge with antigen and with both disease inducing and noninducing fragments.

The foregoing mandate the conclusion that the only thing missing from the specification is the name of ACHR.

But ACHR was patently well known in the field and various ways for isolating it had been described, and multiple references to this effect have been submitted by applicants. Furthermore, the Examiner's reliance on the Merck Manual is not well placed vis-a-vis the claims that require suppression of an autoimmune response since the present claims require that an autoimmune response must have been identified and shown to be suppressed.

It should be emphasized that the absence of autoantibodies from some MG patients does not mean that there is no autoimmune response in the patients. Autoantibodies are only one type evidence of autoimmune response, activated autoreactive T cells are another, increased inflammatory cytokines are a third and so

on. In the present claims, autoimmune response is not used to diagnose the patient as having MG or as being susceptible to MG. It is only used as a marker of the efficacy of the treatment, and its abatement is a goal of the treatment.

For this reason also, the Examiner's reliance on the Merck Manual is not appropriate. A patient within the present claims may have been diagnosed as having MG without ever having been tested for any form of autoimmune response. But the claims require that an autoimmune response be (a) identified and (b) suppressed to assess the efficacy of the treatment. So subject could then be tested to identify an abnormal immune response associated with MG. Hence, there is no failure of description of the claimed subject matter with respect to the patients to be treated. All of the subsisting claims are free of this alleged defect.

Returning to the Examiner's reliance on Fiers, and Amgen applicants comment as follows: in these cases the claimed material, unlike the present claims, was unknown, not a well-published well-characterized antigen. The peptide to which the Examiner refers at p. 6 of the Office Action is in the literature. In Fiers and Amgen the claims were directed to a broad genus based on the description of only one species. The court held that where the genus was both hovel and described solely in functional terms , no generic claim could be permitted based upon description of a single species. In the present instance, applicants have described two species in detail (EAE and AA) and have adduced evidence permitting them to extend the invention to other autoimmune diseases and have named myasthenia gravis as a particular disease to

which the general oral tolerance method can be applied. The inventors did not name ACHR but it was patently known. This is readily distinguishable from Amgen and Fiers. These cases did not address compliance with written description requirement when the claim was drawn to a species of a genus that is described.

Lastly, the Examiner's references to the applicants' response as allegedly containing damning admissions about the present invention are not believed to be appropriate. Applicants said and meant that the subsequent work of the other investigators confirmed that the claimed invention worked as predicted. It is noteworthy that the Examiner has not adduced any literature stating that Drachman, Ma or anyone else failed to make the invention work for years after the filing of the present application. Just because the references are of a later date does not mean that the years between the present filing date and the publications of Drachman's and Ma were due to any gaps in the present specification or in the skill of the art. In any event, the burden to show this is with the Examiner, and this burden the Examiner has not met. The patent law of this country does not prescribe prophetic statements and does not require an achial reduction to practice of every single embodiment of an invention.

Conclusion

Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Howard L. Weiner et. al.

Serial No.: 08/279,275 Art Unit: 1644

Confirmation No.:

Filed: 07/22/94 Examiner: VanderVegt, F.

For: TREATMENT OF AUTOIMMUNE DISEASES BY ORAL ADMINISTRATION OF AUTOANTIGENS

MARK-UP AMENDMENT PURSUANT TO 37 C.F.R. §1.121

24 (Amended) A method of treating myasthenia gravis by suppressing autoimmune response associated with myasthenia gravis comprising orally or enterally administering to a mammalian host in need of treatment an autoantigen specific for myasthenia gravis, [or an autoimmune response-suppressive fragment of said autoantigen,] in an amount effective to suppress said response and thereby to treat said myasthenia gravis.

25 (Amended) A method of suppressing autoimmune response associated with myasthenia gravis comprising orally or enterally administering to a mammalian host in need of treatment an autoantigen specific for myasthenia gravis in an amount effective to suppress said response.

26 (Amended) The method of claim 24 wherein said autoantigen is administered to said host orally.